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EFFECT OF ASPHYXIA DUE TO UMBILICAL CORD OCCLUSION IN THE FOETAL LAMB ON LEAKAGE OF LIQUID FROM THE CIRCULATION AND ON PERMEABILITY OF LUNG CAPILLARIES TO ALBUMIN

BY T. M. ADAMSON, R. D. H. BOYD, JUNE R. HILL, I. C. S. NORMAND, E. O. R. REYNOLDS AND L. B. STRANG

From the Department of Paediatrics, University College Hospital Medical School, London, W.C. 1

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SUMMARY

1. Experiments were performed on foetal lambs, exteriorized at Caesarean section, to determine the effects of asphyxia on the leakage of liquid from the circulation and on the permeability of lung capillaries to albumin. Following a period of control observation (30–120 min) the foetus was asphyxiated by occlusion of the umbilical cord for 5–10 min and then allowed to recover while observations were continued for a further 20–80 min.

2. Measurements were made of the lymph flow from the lungs, that had drained via the thoracic duct; of protein concentration in lymph and plasma; of arterial blood haematocrit, pH, P_{O_2} and P_{CO_2}; and of arterial and left atrial pressures and heart rate. Human serum albumin labelled with ^{125}I was infused intravenously during the control period and ^{125}I count rates were followed in plasma and lymph throughout the experiment. Values for the transfer coefficient of albumin ($\dot{E}/V$ min^{-1}, i.e. interstitial fluid clearance of albumin per unit of lung interstitial fluid volume) were determined during control, cord-occlusion and post-occlusion periods.

3. During cord occlusion arterial and left atrial pressure, haematocrit and plasma protein concentration all rose, returning to the control value by 20 min after release of cord occlusion. The haematocrit values indicated that about 9 % of the blood volume was temporarily lost from the circulation. Lung lymph flow also increased, reaching a maximum in the 5 min period after release of occlusion and returning to the control level 15 min later. Values for $\dot{E}/V$ of albumin were at no time significantly different from those during the control period.

4. It was concluded that acute foetal asphyxia produced by umbilical

cord occlusion caused an increased leakage of liquid from the circulation in general. This effect was temporary and was probably due to an increase in capillary pressure during cord occlusion. The asphyxia had no persistent effect on the permeability of lung capillaries to albumin.

INTRODUCTION

Asphyxia or hypoxia alone has been shown to cause an increase in lymph flow and in protein transfer to lymph drained from the lungs (Warren & Drinker, 1942; Warren, Peterson & Drinker, 1942) and from other tissues (Maurer, 1940, 1941). From these experiments and from a variety of others in which an increased leakage of liquid from capillaries in response to severe hypoxia or asphyxia can be inferred, the suggestion has often been made that lack of oxygen causes an increase in permeability due to damage to the endothelium of capillary walls (Landis, 1928; Pochin, 1942; Hendley & Schiller, 1954). But Courtice & Korner (1952) and Korner & Courtice (1954) favour an alternative explanation that a rise in capillary pressure, taking place as part of complex cardiac and vascular changes in response to hypoxia, of itself causes leakage from the circulation with no real change in permeability. It seems likely that if the first explanation is correct the increase in leakage would persist after the hypoxic episode was over, until the damage to the capillaries had been repaired; if the second, then capillary leakage would rapidly revert to normal after cessation of hypoxia.

The possibility that severe asphyxia of the foetus before delivery could cause an increase in the permeability of lung capillaries to proteins persisting into the new-born period is of particular interest as a possible cause in the new-born baby of abnormal conditions, such as hyaline membrane disease and haemorrhagic pulmonary oedema, in which plasma proteins have been shown to accumulate in extravascular spaces of the lung (Gitlin & Craig, 1956; Gajl-Peczalska, 1964; Adamson, Boyd, Normand, Reynolds & Shaw, 1969). The aim of the experiments on the foetal lamb reported here was to investigate the effects of severe asphyxia on losses of liquid from the circulation in general and the lung circulation in particular; and to find out whether a persisting effect on the permeability of lung capillaries to albumin was brought about by an episode of asphyxia. In reviewing published work on the effect of asphyxia on capillary permeability, Landis & Pappenheimer (1963) conclude that a severe degree of hypoxia is necessary to produce a demonstrable effect. To produce a sufficiently extreme degree of hypoxia the placental circulation was stopped completely by umbilical cord occlusion for the longest period compatible with survival, viz. between 5 and 10 min.

METHODS

Anaesthesia and monitoring of ewe. Experiments were performed on exteriorized foetal lambs for which exact tupping dates were not available; mean weight 4·5 kg (range 2·04–6·75 kg) and mean crown rump length 48·2 cm (range 38–59 cm). From these weight and length measurements the foetuses were judged to range in gestation from about 125 days to term (147 days). In eight experiments performed during one season the ewe was anaesthetized with pentobarbitone, as previously reported (Humphreys, Normand, Reynolds & Strang, 1967). In fifteen further experiments, performed during the following season, thiopentone was given intravenously and inhalation anaesthesia maintained with halothane, using a closed circuit and artificial ventilation. The general technique for maintenance of the ewe, exteriorization and monitoring of the foetus followed Howatt, Humphreys, Normand & Strang (1965) and Humphreys *et al.* (1967).

Experimental procedure and measurements in foetus. In twenty experiments, after a period of control observations (range 30–120 min) the umbilical cord was occluded for a period of 5–10 min by digital compression, and observations were continued for 20–80 min after release of occlusion. To obtain these twenty experiments we did a total of thirty-three, but the remainder did not survive cord occlusion. In all these experiments foetal heart rate, blood pressure, P_{a,O_2}, P_{a,CO_2}, pH_a and rectal temperature were measured. In seven of these experiments the left atrial pressure was measured by a pressure transducer (Sanborn) connected to a polyethylene cannula introduced through the wall of the left atrium and secured by a purse string suture; the zero reference point being mid-atrium. In nine of these experiments haematocrit was measured in samples of carotid artery blood using 75 mm heparinized capillary tubes (i.d. 1 mm) centrifuged at 22,500 g for 10 min, the values obtained being the mean of paired samples (which differed by less than 4 %). In eight of these experiments total protein concentration was measured in plasma as described by Boyd, Hill, Humphreys, Normand, Reynolds & Strang (1969).

In sixteen of these experiments the thoracic duct component of lung lymph was collected as described by Humphreys *et al.* (1967), into plastic tubes over timed intervals up to 10 min in duration, and the volume measured by weighing, assuming a specific gravity of 1·0. In nine of these latter experiments total protein in lymph was measured as described by Boyd *et al.* (1969).

In four experiments a second cord occlusion was performed after recovery from the first occlusion. The thorax had to be opened in the course of the dissection to enable lymph to be collected; in one animal it was closed up again before the first occlusion but opened again for the second; in another animal the first occlusion was done as usual with the chest open, but the thorax was closed for the second occlusion. Closure of the chest was effected by suturing together the split sternum and overlying skin and inserting a saline soaked swab in the thoracic inlet; its effectiveness was measured by recording negative pleural pressures during the gasping efforts which followed cord occlusion. In two experiments 3–5 ml. 1 % Evans blue was injected through a tracheal cannula and mixed with the liquid which fills the foetal lung.

In four additional experiments not included in the Table in Results and in which no lymph was collected, main pulmonary artery pressure was measured by a pressure transducer (Sanborn) connected to a polyethylene cannula introduced through the wall of the right ventricle and advanced into the main pulmonary artery.

Infusion of radioactively labelled albumin. It was originally our intention to infuse [^{125}I]albumin, maintaining a constant plasma level, during a control period and to compare the results with those obtained from a similar infusion of [^{131}I]albumin given during and after cord occlusion. But it was found impossible to maintain plasma levels of [^{131}I]albumin constant enough to employ the method of analysis originally chosen, and the results are therefore confined to analysis of ^{125}I alone.

In eleven experiments after lymph flow was established at a steady level, a solution of 15–20 μc [^{125}I] human serum albumin ([^{125}I]H.S.A. from the Radiochemical Centre, Amersham) was infused for 30 min during the control period, through a polyethylene cannula advanced from the external jugular vein into the superior vena cava. [^{125}I]H.S.A. was delivered by an infusion pump (Harvard Apparatus Co.), the rate of infusion being progressively decreased so that during the infusion period a steady plasma level was achieved (S.D. $< 3{\cdot}6\,\%$ of mean in ten experiments). The infusion was stopped before cord occlusion. Samples of lymph and plasma were collected at intervals throughout the experiment, centrifuged and counted to an S.D. of 6 % or less in a well-type scintillation counter as described by Boyd *et al.* (1969).

RESULTS

Tables 1 and 2 summarize effects observed before, during and after the first period of cord occlusion in twenty experiments. A second cord occlusion in four of them produced very similar results; and no difference was observed in the two experiments in which the chest was closed for one occlusion but open for the other. In two experiments in which Evans blue was introduced into alveolar liquid no dye was detectable in lymph before or following cord occlusion. In four experiments not included in the Tables, simultaneous measurements of carotid artery and pulmonary artery pressures during brief periods of cord occlusion (up to 2 min) showed no differences, within ± 2 mm Hg between these pressures.

Effects of cord occlusion on $P_{\mathrm{a,CO_2}}$, $P_{\mathrm{a,O_2}}$, $p\mathrm{H_a}$, cardiovascular pressure and heart rate

Fig. 1 gives results from a typical experiment in which, following a period of control observations, the umbilical cord was occluded for 6 min and then released. The pattern of changes in heart rate, carotid arterial B.P. and in $P_{\mathrm{a,O_2}}$, $P_{\mathrm{a,CO_2}}$ and $\mathrm{pH_a}$ and their mean values were similar to those reported by Howatt *et al.* (1965). Left atrial pressure (LAP), which was not measured by Howatt *et al.* (1965), increased from a pre-occlusion level of 1·0 mm Hg to a peak of 7 mm Hg at the third minute of occlusion. A similar rise in LAP was observed in each of the seven experiments in which this measurement was made. Mean values for vascular pressures and heart rate are given in Table 1; just before release of cord occlusion mean value for $P_{\mathrm{a,O_2}}$ was 8·4 mm Hg, for $P_{\mathrm{a,CO_2}}$ 92 mm Hg and $\mathrm{pH_a}$ 6·91.

Haematocrit and plasma protein concentration of arterial blood

Fig. 1 and Table 2 show that haematocrit and plasma protein concentration both increased during cord occlusion. Following release of occlusion the haematocrit decreased slowly, reaching the pre-occlusion value after

20 min; plasma protein concentration declined more rapidly and by 5 min had regained the pre-occlusion level.

Lung lymph flow

After the onset of cord occlusion in fourteen experiments a rise in the thoracic duct component of lung lymph flow took place, generally reaching a maximum shortly after release of occlusion (see Figs. 1 and 2). In four experiments the maximum occurred during occlusion and in ten after its release. Table 2 gives mean values for lymph flow and lymph protein

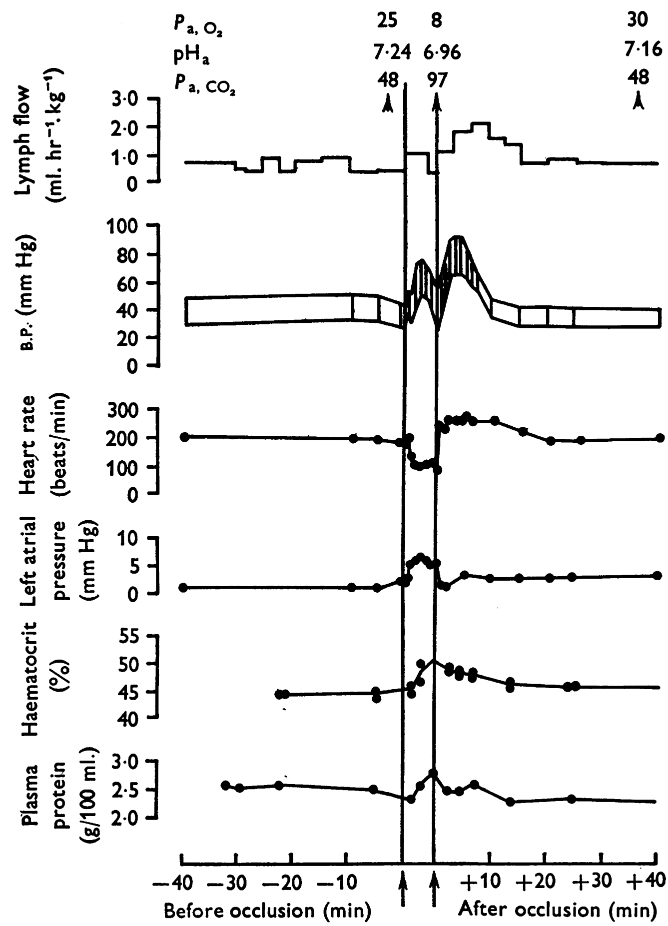

Fig. 1. Foetal lamb expt. Body weight = 5·5 kg. Values of P_{a, O_2} (mm Hg), P_{a, CO_2} (mm Hg), pH_a, lymph flow (ml./hr.kg), arterial blood pressure (mm Hg), heart rate (beats/min), left atrial pressure (mm Hg), haematocrit (%) and plasma protein concentration (g/100 ml.) against time (min). Cord occlusion was applied for a period of 6 min between arrows on the abscissal scale.

concentration and indicates the significance of the differences from pre-occlusion values where they exist.

Transfer of radioactively labelled albumin from plasma to lung lymph via pulmonary interstitial fluid space

Fig. 2 gives results from one of the eleven similar experiments in which [^{125}I]H.S.A. was infused intravenously during the control period, and count rates of plasma and lymph samples collected throughout the experiment were determined.

TABLE 1. Mean values ($\pm$ S.E. of mean) of B.P., heart rate and left atrial pressure, before, during and after umbilical cord occlusion. During occlusion the values are the maximum (Max) and last values before cord release (End)

		Before occlusion	During occlusion Max	During occlusion End	After occlusion At 5 min	After occlusion At 15 min
Blood pressure (mm Hg)	Mean	46	69	35	63	41
	S.E. of mean	1·3	2·4	2·5	2·6	1·6
	n	20	20	20	17*	16*
Heart rate (beats/min)	Mean	202	200	95	240	207
	S.E. of mean	10	9·3	5·5	8·9	13
	n	19	19	19	16	15*
Left atrial pressure (mm Hg)	Mean	2·0	7·7	6·1	3·1	2·9
	S.E. of mean	0·4	1·2	1·3	0·4	0·4
	n	7	7	7	7	6*

* Exact measurements at these times not available in one to four experiments.

The analysis of these experiments is based on a simple model (cf. Boyd *et al.* 1969), in which it is assumed that the interstitial fluid space (I.F.S.) is a well stirred single compartment of volume, V ml. Lymph drains from I.F.S. and the concentration of a substance S (in this case plasma albumin) is assumed to be the same in lymph (C_L) and interstitial fluid (C_I), providing allowance is made for a time lag ($t_R \approx$ 3–5 min) that occurs between the moment a given sample leaves I.F.S. and its appearance as lymph at the collection point (i.e. C_I at time $t = C_L$ at time $t+t_R$). In the equations, C_L corrected for t_R is used in place of C_I. The amount of S entering I.F.S. per unit time is $\dot{G}\,C_P$ (where $\dot{G}$ = inflow clearance constant, ml./min, and C_P = plasma concentration) and the amount leaving is $\dot{E}C_L$ (where $\dot{E}$ = outflow clearance constant, ml./min).

$$\frac{dS}{dt} = \frac{VdC_L}{dt} = \dot{G}C_P - \dot{E}C_L,$$

$$\frac{dC_L}{dt} = \frac{\dot{G}}{V}\,C_P - \frac{\dot{E}}{V}\,C_L,$$

where C_P is constant, at equilibrium:

$$\frac{\dot{G}}{V}C_P = \frac{\dot{E}}{V}C_L \quad \text{and} \quad \frac{C_L}{C_P} = \frac{\dot{G}}{\dot{E}} = r.$$

The C_L/C_P ratio for the animals own plasma albumin has been previously determined in other experiments under circumstances similar to the control period in the present experiments, where steady-state equilibrium conditions apply, and the mean value obtained, $r = 0{\cdot}77$ (see Boyd *et al.*

TABLE 2. Mean values ($\pm$ S.E. of mean) of lung lymph flow ($\text{ml.hr}^{-1}.\text{kg}^{-1}$) haematocrit (%) and plasma protein concentration (g/100 ml.) before, during and after 5–10 min umbilical cord occlusion

		Control minutes before occlusion		Cord occlusion	Minutes after occlusion			
		45–5	5–0		0–5	5–10	10–20	20–30
Lung lymph flow ($\text{ml.hr}^{-1}.\text{kg}^{-1}$)	Mean	1·16	1·17	1·84*	2·14*	2·05*	1·38*	1·14
	S.E. of mean	0·18	0·20	0·19	0·17	0·14	0·17	0·17
	n	16	16	16	16	16	16	16
Lymph protein concentration (g/100 ml.)	Mean	2·23	2·26	2·26	2·28	2·23	2·21	2·11
	S.E. of mean	0·10	0·10	0·10	0·09	0·10	0·10	0·09
	n	9	8	9	9	9	9	9
Haematocrit (%)	Mean	46·4	48·8	51·9*	50·7*	50·2*	50·4†	47·8
	S.E. of mean	2·3	1·9	2·3	2·4	1·9	1·7	2·2
	n	9	8	9	9	9	7	8
Plasma protein concentration (g/100 ml.)	Mean	2·95	2·97	3·17*	3·03	2·87	2·88	2·60
	S.E. of mean	0·25	0·28	0·23	0·21	0·16	0·26	0·12
	n	8	7	8	8	5	8	6

* Individual paired differences from mean pre-occlusion value significantly different from zero at $P < 0{\cdot}002$.

† Individual paired difference from mean pre-occlusion value significantly different from zero at $P < 0{\cdot}02$.

1969, Table 2, mature foetal lambs) has been used to enable $\dot{E}/V$ of albumin (transfer coefficient, min^{-1}) to be determined.

$$\left.\begin{aligned} \frac{\mathrm{d}C_L}{\mathrm{d}t} &= \frac{\dot{E}}{V}(rC_P - C_L). \\ \text{Integrating:} \qquad C_L &= \frac{\dot{E}}{V}\int(rC_P - C_L)\mathrm{d}t, \end{aligned}\right\} \qquad (1)$$

or for the case where rC_{P} = constant, as during the control period,

$$\left.\begin{aligned} C_{\mathrm{L}} &= rC_{\mathrm{P}}\,(1-\mathrm{e}^{-\dot{E}t/V}),\\ -\frac{\dot{E}t}{V} &= \log_e\left(1-\frac{C_{\mathrm{L}}}{rC_{\mathrm{P}}}\right). \end{aligned}\right\} \qquad (2)$$

Figure 3*A* shows a plot of $\log_e(1-C_{\mathrm{L}}/rC_{\mathrm{P}})$ against time, the linearity of which demonstrates the appropriateness of the model. The line was fitted

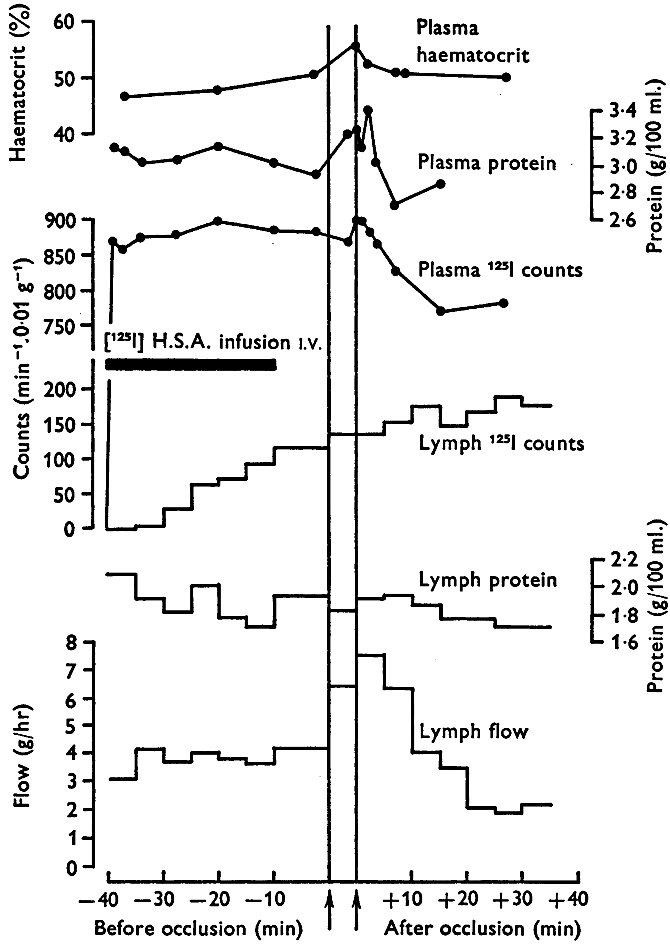

Fig. 2. Foetal lamb expt. Body weight = 4·7 kg. Count rates in plasma and lung lymph of [^{125}I]H.S.A. against time (min). The period of H.S.A. infusion is shown. Values for plasma haematocrit (%) and protein concentration (g/100 ml.) are also shown above, and below, lymph protein concentration (g/100 ml.) and flow (g/hr). Cord occlusion was applied for 5 min between the arrows.

to the points by least squares ($r = 0{\cdot}99$, $y = 0{\cdot}069 - 0{\cdot}0099x$) its slope gives the value for $-\dot{E}/V$ of albumin. To demonstrate the reality of t_R in this particular plot C_L was not corrected; t_R appears as the interval ($\approx$ 6 min) between zero time and the intercept of the regression line with the abscissae.

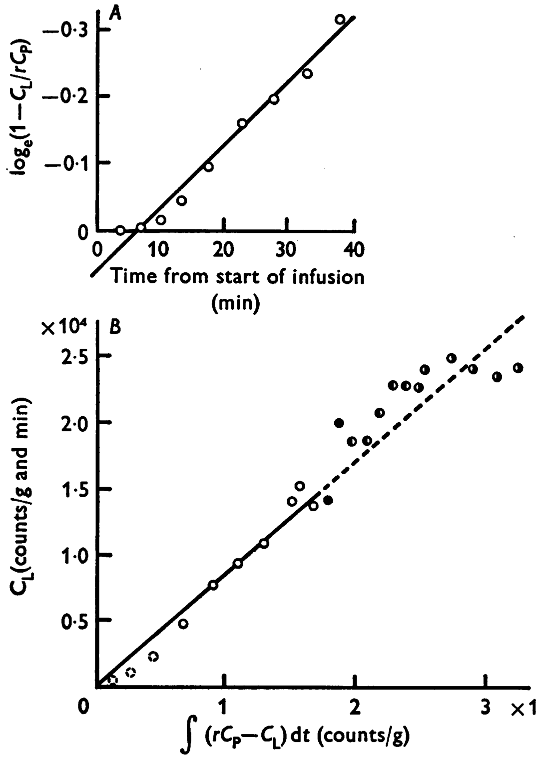

Fig. 3. Foetal lamb expt. Body weight = 5·2 kg. *A*. $\text{Log}_e(1 - C_L/rC_P)$ plotted against time (min) from start of [^{125}I]H.S.A. infusion. ○ indicate that the data came from the control (pre-occlusion) period only. Slope = $-\dot{E}/V = -0{\cdot}0099\ \text{min}^{-1}$.

B. C_L corrected for t_R (counts/min.g) plotted against $\int(rC_P - C_L)\,dt$ (counts/g). ○ control period; ● during cord occlusion (duration 6 min); ◐ 0–20 min after release of cord occlusion; ◑ 20–80 min after release of cord occlusion. The continuous line defines the mean slope of the seven complete open circles, its slope = $\dot{E}/V = 0{\cdot}0084\ \text{min}^{-1}$. ($\dot{E}/V$ is a measure of permeability to albumin in terms of transfer coefficient, min^{-1}. See text for further explanation.)

In Fig. 3*B* the open circles show the same data treated differently, here C_L (corrected for t_R) has been plotted against $\int(rC_P - C_L)dt$ obtained by numerical integration (trapezoidal approximation). Again a linear plot is obtained, its slope ($= 0{\cdot}0084\ \text{min}^{-1}$) gives a similar value for $\dot{E}/V$ of albumin to that obtained above. From the ten experiments in which both methods of integration could be applied to data for the control period, paired values for $\dot{E}/V$ were obtained; a t test on the paired differences demonstrated that the use of the numerical integration (equation (1)) to obtain $\dot{E}/V$ did not introduce any systematic bias as compared with the mathematical solution (eqn. (2)) since the mean of the paired differences was not significantly different from zero ($0{\cdot}3 < P < 0{\cdot}4$). Table 3 gives

TABLE 3. Values for $\dot{E}/V \times 10^2$ (min^{-1}) of [^{125}I]H.S.A.

	Control period		During cord occlusion	0–20 min after release of cord occlusion	> 20 min after release of cord occlusion
	a	*b*	*c*	*d*	*e*
Mean	1·01	0·92	0·87	0·93	0·97
n	10*	11	11	11	10
S.D.	0·44	0·47	0·35	0·43	0·43
S.E. of mean	0·14	0·14	0·11	0·13	0·13

First column in control period (a) calculated from the values for $-\dot{E}/V$ obtained from slope of regression of $\log_e (1 - C_L/rC_P)$ on time, see Fig. 3*A*. (*C_P not constant in one animal.) Second column in control period (b) and remaining columns calculated from the means of $\dot{E}/V$ values obtained from $C_L/\int(rC_P - C_L)dt$, see Fig. 3*B*. (Value for $r = 0{\cdot}77$ has been used throughout, see text.) The mean of the individual paired differences is not significantly different from zero when columns (a) and (b) ($0{\cdot}3 < P < 0{\cdot}4$), ($b$) and ($c$) ($0{\cdot}4 < P < 0{\cdot}5$), ($b$) and ($d$) ($0{\cdot}8 < P < 0{\cdot}9$) and ($b$) and ($e$) ($P \approx 0{\cdot}99$) are compared using a t test.

$\dot{E}/V$ values obtained by the two methods during the control period, and by numerical integration alone for the occlusion and post-occlusion periods. It shows, as does Fig. 3*B*, that cord occlusion did not produce a significant change in the value for the transfer coefficient of albumin.

DISCUSSION

Amount of liquid lost from circulation and increase in lung lymph flow

We estimate, from the increase in haematocrit during cord occlusion, that the average maximal reduction in blood volume was about 9 %; and so we calculate, using Barcroft & Kennedy's (1939) value of 120 ml./kg for blood volume (excluding placenta), that on average about 11 ml./kg of liquid was lost from the circulation. The fact that plasma protein and [^{125}I]H.S.A. simultaneously rise suggests that the average concentration of protein in the extra liquid lost from the circulation was lower than in plasma. The mean value for the cumulative extra volume of lymph above the control level was 0·34 mg/kg which is 3% of our estimate for the total liquid lost from the circulation. As the foetal lungs, excluding the liquid contained in the future airways and alveoli, average about 2·5% of body weight (Humphreys *et al.* 1967, Fig. 12), the extra amount of liquid lost from the pulmonary circulation and collected as lymph is of the same order, in proportion to tissue weight, as the loss from the circulation as a whole.

Effect of changes in vascular pressures

Because low resistance communications exist between the two circulations, systemic and pulmonary vascular pressures are very similar, and we have found that this continues to be so during cord occlusion. Since vascular pressures on both the arterial and venous sides of the pulmonary circulation rose during cord occlusion, it is very likely that pulmonary capillary pressure rose, which could by itself account for the increased leakage from the pulmonary circulation, and no change in permeability of capillary walls need be inferred. Boyd *et al.* (1969) concluded that due to vasoconstriction, pulmonary capillary pressure and lymph flow were higher in the normal unasphyxiated foetus than in the new-born. Our experimental results fit in with the idea that asphyxia provokes temporarily a further exaggeration of these foetal characteristics.

Permeability of lung capillaries to albumin

Since our experimental results do not provide us with measurements of the area of lung capillary surface available for exchange, or of interstitial volume, we have expressed permeability to albumin as a transfer coefficient, $\dot{E}/V$ min^{-1}, i.e. interstitial fluid clearance per unit of interstitial volume. To determine $\dot{E}/V$ from eqns. (1) and (2) it is necessary to know the value for r, the steady state equilibrium lymph/plasma ratio for albumin. The value we have used is strictly correct for the control period only, but during cord occlusion with its accompanying rise in capillary pressure, hydrodynamic flow across capillary walls and lymph flow are increased and a steady state no longer exists. From capillary pore theory the value of r can be expected to decrease as hydrodynamic flow increases (Landis & Pappenheimer, 1963). However, the value of r for albumin during cord occlusion is impossible to obtain experimentally. In calculating albumin transfer for the period during and immediately after cord occlusion we have used the steady-state equilibrium value of r (0·77) which might tend to underestimate $\dot{E}$; in the same period V almost certainly increases temporarily (though probably by only a few per cent) leading also to a reduction in the $\dot{E}/V$ value obtained. The absence of a significant change in our estimates for $\dot{E}/V$ of albumin seems to indicate that interstitial fluid clearance of albumin ($\dot{E}$) increased during cord occlusion as might be expected, since lymph flow rose without any appreciable change in its total protein concentration.

By 20 min after release of cord occlusion lymph flow, haematocrit, plasma protein concentration and vascular pressures had returned to pre-occlusion levels, and since the protein concentration in lymph did not change at any time, we can justifiably assume that a steady state had been restored, with return of V and r to their former levels. $\dot{E}/V$ values of albumin calculated for the period commencing 20 min after release of cord occlusion were compared with those obtained during the control period (Table 3), and the fact that no significant difference could be demonstrated is good evidence against any persistent effect of cord occlusion on capillary permeability to albumin. The effect of asphyxia on the leakage of liquid and proteins from the circulation is probably confined to the asphyxial period, and due essentially to changes in vascular pressures.

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